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Sensory cortical re-mapping following upper-limb amputation and subsequent targeted reinnervation: A case report

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ABSTRACT

This case study demonstrates the change of sensory cortical representations of the residual parts of the arm in an individual who underwent a trans-humeral amputation and subsequent targeted reinnervation (TR). As a relatively new surgical technique, TR restores a direct neural connection from amputated sensorimotor nerves to specific target muscles. This method has been successfully applied to upper-limb and lower-limb amputees, and has shown effectiveness in regaining control signals via the newly re-innervated muscles. Correspondingly, recent study results have shown that motor representations for the missing limb move closer to their original locations following TR. Besides regaining motor control signals, TR also restores the sensation in the re-innervated skin areas. We therefore hypothesize that TR causes analogous cortical sensory remapping that may return closer to their original locations. In order to test this hypothesis, cortical activity in response to sensory-level electrical stimulation in different parts of the arm was studied longitudinally in one amputated individual before and up to 2 years after TR. Our results showed that 1) before TR, the cortical response to sensory electrical stimulation in the residual limb showed a diffuse bilateral pattern without a clear focus in either the time or spatial domain; and 2) 2 years after TR, the sensory map of the reinnervated median nerve reorganized, showing predominant activity over the contralateral S1 hand area as well as moderate activity over the ipsilateral S1. Therefore, this work provides new evidence for long-term sensory cortical plasticity in the human brain after TR.

1. Introduction

Changes in cortical mapping begin seconds after the loss of the limb and can continue to change years after the injury (Kaas et al., 1983; Merzenich et al., 1983; Merzenich and Jenkins, 1993). Previous studies have found that following upper extremity amputation, cortical sensory representations for the adjacent intact areas extend to cortical regions corresponding to the absent hand (Elbert et al., 1997; Grusser et al., 2001). Other studies have found that in human arm amputees, the cortical reorganization contralateral to the amputation spreads bilaterally to both hemispheres (Bjorkman et al., 2007a,b).

After immediate hand replantation and long-term hand transplants, hand function recovery has been reported to be associated with cortical reorganization. Although results related to motor cortical reorganization following repair are more readily available, few studies have reported sensory cortical reorganization on human subjects after nerve repair (Bjorkman et al., 2007a,b; Blume et al., 2014). In previous studies from Bjorkman et al. (2007a,b), sensory cortical remapping on one patient who underwent an immediate surgical hand replantation was reported. Twelve months after the surgery, the primary somatosensory cortex was found to reorganize with the activation pattern to be more bilateral compared to an able-bodied hand (Bjorkman et al., 2007a). Two years after the surgery, predominantly contralateral somatosensory cortex activation was reported (Bjorkman et al., 2007b). Similarly, animal studies reported that median nerve regeneration in adult owl monkeys showed the reestablishment of topographic representations for localized skin areas, although in a limited extent (Wall et al., 1986). These results provided evidence for reorganization of cortical sensory representation to a pattern closer to the 'intact' case after nerve repair.

As a relatively new surgical approach following amputation, targeted reinnervation (TR) provides a novel and fundamentally different way for nerve repair in that it denervates specific muscles and skin regions (Kuiken, 2003; Kuiken et al., 2004; Hijjawi et al., 2006), and then reinnervates them with the residual nerves of the amputated limb. After TR, the reinnervated muscles can act as a natural biological amplifier to enhance the efferent motor command signal, allowing for the control of a multi-degree of freedom myoelectric prosthesis. As

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compared to transplantation, TR is less costly, requires less time in hospital and for recovery, and can be applied to a wider amputee population (see a review for the comparison between transplantation and TR (Agnew et al., 2012)). It has been demonstrated that several months after TR, new functional connections between the nerves and muscles can be created, which restores motor function (Agnew et al., 2012). Correspondingly, a close to 'normal' motor cortical map for the missed limb related to motor task performance can be re-established (Chen et al., 2013). Besides recovery of motor function, TR also causes return of sensations of touch, pressure, vibration and temperature for the missing limb of the skin overlying reinnervated muscles (Kuiken et al., 2007a,b; Marasco et al., 2009). If indeed cortical restoration of original spatial maps is an important metric for the effectiveness of a restoration method, it will be of great importance to test whether TR successfully restores the sensory cortical representation as well. However, both short-term and long-term cortical changes in spatial mapping associated with TR-induced sensory recovery are still unknown. To answer this question, we used high-density electroencephalography (EEG) to identify and quantify cortical activity in response to stimulating the middle finger of the intact limb and the residual median nerve of the amputated limb in one session before and three sessions after targeted reinnervation surgery in an individual who underwent TR.

2. Methods

2.1. Subject

A 24-year-old, right hand dominant male, who sustained a traumatic injury and a left trans-humeral amputation in July 2007, was recruited for this study. The subject has used a prosthesis since October of 2007. He wears it for several hours a day and uses it to help him hold objects, fold clothes, drive and open letters. Initially post-operation, he reported that he had some phantom limb sensation. However, when we recruited him in 2008, he said that the phantom limb pain was gone, and that he only occasionally experienced phantom limb sensation and that this was not bothersome to him. The first set of experimental data were collected in August 2008, 1 week before his targeted reinnervation (TR) surgery. As shown in Fig. 1, during the TR surgery, the median nerve was transferred to the medial head of the biceps; the distal radial nerve was transferred to the lateral head of the triceps; and the ulnar nerve was transferred to the motor reinnervation point of the brachialis. Subcutaneous fat was removed over the biceps and triceps to increase the EMG signal magnitude for subsequent myoelectric control. The fat removal denervated some of overlying skin enabling hand afferents to reinnervate the participant's skin after several months. When this section of skin was touched after reinnervation occurred, he felt his missing hand. Post-TR, three sets of data were collected in January and July of 2009 and June 2010.

To verify the reliability of our experimental protocol and data processing, we also recruited one age-matched able-bodied right hand dominant control participant (age: 24 years old). Two sets of data were collected in the able-bodied control participant on March 23rd, 2010 and April 13th, 2010.

All studies were approved by the Institutional Review Board of Northwestern University and in compliance with the principles of the Declaration of Helsinki with written consent provided by the participants prior to participation.

2.2. Experimental protocol

In each of the participants, we first searched for the stimulation site and intensity using constant current square-wave pulses that were delivered by a Compex II stimulator (Compex Medical SA, Ecutens, Switzerland) with pulse width at 0.3 ms long, and interstimulus interval at 200 ms. When determining the stimulation site, we searched for the location where the subject felt the most focused sensation of one of the four fingers. Then, the intensity was set to the highest amplitude that the participant could tolerate without losing focus or causing discomfort, pain, or detectable muscle contractions. The amputee subject reported the strongest and most focused sensation of the tip of his missing middle finger when stimulating the reinnervated median nerve site, although also with faint sensation of his thumb and elbow. As reference, we also recorded somatosensory-evoked potentials (SEPs) while stimulating the tip of his middle finger from the intact side. For each site, 2000–3000 trials of SEPs were recorded in 2 or 3 blocks of 1000, with at least 5 min of resting time between each block. During all of the experiments, the amputee participant remained relaxed and tried to avoid eye movements. The middle finger from the

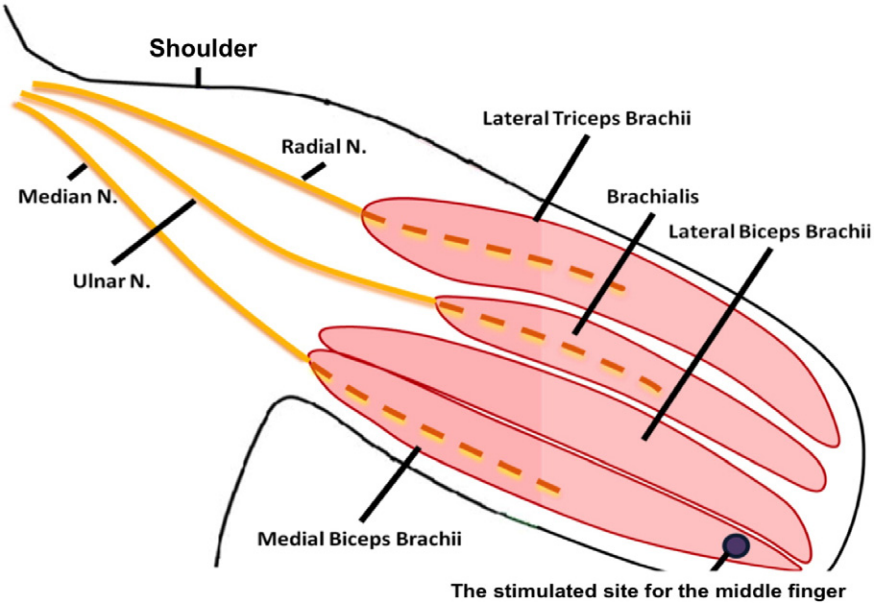

Fig. 1. Schematic of the targeted reinnervation (TR) procedure for the amputee subject.

Table 1
The experiment on different sessions.

Session #	1	2	3	4
Date	08/2008[a]	01/2009	07/2009	06/2010
Amputated side	MN (DNS) (Fig. 1 right)	MN(DNS) (Fig. 1 right)	MN(DNS) (Fig. 1 right)	MN(CS) (Fig. 2 left)
Intact side	N/A	MF(CS)	MF(CS)	MF(CS)

[a] This was about 1 year after amputation (07/2007) and 1 week before TR. MF—middle finger, MN—median never, CS—cutaneous stimulation, and DNS—direct nerve stimulation.

intact hand was stimulated via cutaneous stimulation, and the residual median nerve at the amputated side was stimulated using direct nerve stimulation via a needle electrode during all but the last experiment (see Table 1 for the summary of the experiments on different dates). Because the participant was scheduled for surgery to remove a neuroma 2 days after the last experiment, we used cutaneous stimulation of his reinnervated median nerve close to the elbow to reduce the risk of infection. The exact stimulation sites via needle and cutaneous electrodes for the median nerve are shown in Fig. 2.

In an effort to test for the consistency of our approach, we also recorded SEPs associated with finger stimulation in one age-matched able-bodied control participant on two different days. This able-bodied participant reported most focused sensation when we stimulated the ulnar nerve in both arms via needle electrodes applied at the elbow as well as via cutaneous electrodes applied at the little finger (see Fig. 3 for the stimulation sites). Therefore, we recorded SEPs while stimulating the two-side little fingers via cutaneous stimulation, and two-side ulnar nerves via need electrodes.

2.3. Experimental data collection

High-density (128 channels) scalp EEG Data were collected at 4 kHz. EEG electrode positions and the anatomical landmarks (nasion and two preauricular points) were recorded using a 3D magnetic digitizer (Polhemus, Colchester, VT). The digitized electrode locations were used to co-register the EEG data with the participant's anatomical MRI. T1-weighted MR images were taken with a 3 T Siemens MAGNETOM Trio scanner (Siemens AG, Erlangen, Germany) at Northwestern Memorial Hospital. Approximately 176–192 contiguous images in the sagittal plane were taken, with voxel dimensions of $1.0 \times 1.0 \times 1.0$ mm and voxel matrix of 256×256.

2.4. Data processing

EEG signals were screened for the presence of eye and muscle movement artifacts in any of the channels, which eliminated that signal in an individual trial from further analysis. The remaining trials were aligned by the down-phase of the stimulation artifact, segmented (−20–50 ms, with 0 respect to the down-phase of the stimulation artifact), baseline (−20 to −5 ms) corrected, and averaged for each channel. The averaged EEG signals were down-sampled to 256 Hz and imported into the CURRY software environment (Version 5.0, Compumedics Neuroscan, Charlotte, NC) for reconstruction of the cortical activity.

In CURRY software, a subject-specific boundary element method (BEM) model was built based on the participant's anatomic MRI data. The BEM model was composed of three compartments for the skin, skull, and brain with 10.0, 9.0, and 7.0 mm resolution, respectively. Coefficients of conductivity used for each compartment were 0.25 S/m for skin, 0.017 S/m for skull, and 1.79 S/m for brain (Yao and Dewald, 2005). The input EEG data were baseline (−20 to −5 ms) corrected, and then co-registered to the reconstructed skin by superimposing the locations of anatomical landmarks (nasion and two preauricular points). The Low Resolution Electromagnetic Tomography (LORETA) method with the parameter Lp = 1 was chosen as the inverse method to localize cortical generators from the scalp EEG potentials (Pascual-Marqui et al., 1994, 2002). All the sources were constrained on the segmented cortex with the spatial resolution as 3 mm, and perpendicular to the surface of the cortex. This method has been shown to provide better source localization ability than moving dipoles and minimum norm methods (Yao and Dewald, 2005; Grova et al., 2006; Bai et al., 2007). Current density strengths were measured in units of $\mu A/mm^2$.

Current density reconstructions exported from CURRY were loaded into MATLAB (The Mathworks, Natick, MA) for further processing and analysis. In Matlab, the region of interest (ROI), consisting of bilateral primary somatosensory cortices (S1) for sensory representations, was manually chosen by a well-trained neuroscientist based on the participant's anatomical MRI data. The MATLAB routine then automatically extracted all sources from the current density reconstructions that resided in this region. Bilateral S1 areas were further divided into segments from medial to lateral, each being 10 mm long. This processing allows us to represent the bilateral S1 using location indices, where negative and positive 1–10 indicate segments on ipsilateral and contralateral side S1, respectively, all from medial to lateral (see the top of Fig. 4a). At each of the time point, cortical activity on each of these segments was voxel-averaged and normalized to the maximum during the 10–40 ms window. Using the above method, a time-location distribution (with time resolution of 3.9 ms and spatial resolution of 1 cm) of cortical activity on bilateral S1 over 10–40 ms time window was created.

Additionally, we quantified the peak location of cortical activity and whether it has a diffused or focused pattern. In an effort to do this, we first summed the distribution along the time axis, and thus obtaining a 'location curve' along the bilateral S1 location indices. This location-curve showed the accumulated activity at each location during the whole 10–40 ms time window. The peak location was defined as the location with the strongest accumulated strength over bilateral S1 cortices. The diffusion/focus of the activity was quantified on each side of S1 by the value of quality (i.e., the *Q*-value). The *Q*-value is commonly used in describing the quality of a band-pass filter, which is calculated as the peak value of a response divided by the bandwidth. A big *Q*-value means a very focused response, while a low *Q*-value indicates a diffused response. When applying the *Q*-value for quantification of the diffusion/focus of cortical activity, we first normalized the location-curve; then on each hemisphere's S1, we identified the peak and the bandwidth to calculate the *Q*-value over one side of S1.

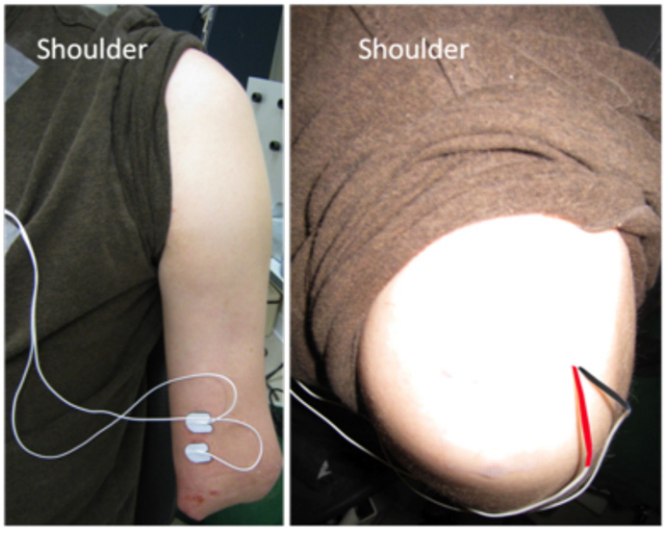

Fig. 2. The stimulation sites via cutaneous (left) and needle (right) electrodes for the median nerve on the amputee participant.

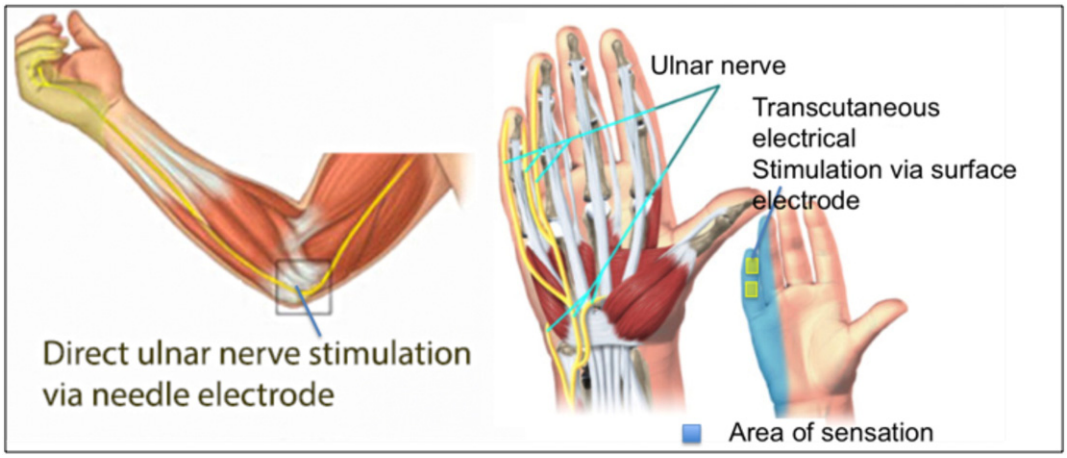

Fig. 3. Schematic of the site of ulnar nerve stimulation via a needle electrode (left) and the surface electrode location (right) over the little finger in the able-bodied control participant.

3. Results

3.1. Results from the able-bodied control participant

As shown in Fig. 4 and the green open markers in Fig. 6, able-bodied participant's results are consistent between the two different sessions and between different stimulation methods. The stimulation causes responses mostly in the contralateral S1. As shown in Fig. 6, the peak locations in the able-bodied participant (green ellipses) are consistently located in the range between 4 and 7, which is in agreement with finger and hand areas on the contralateral S1. The maximum error in the peak location, between different sessions but with the same method or between different methods but with the same day, is 1 location index (10 mm) in the able-bodied participant. Fig. 6 also shows that cortical

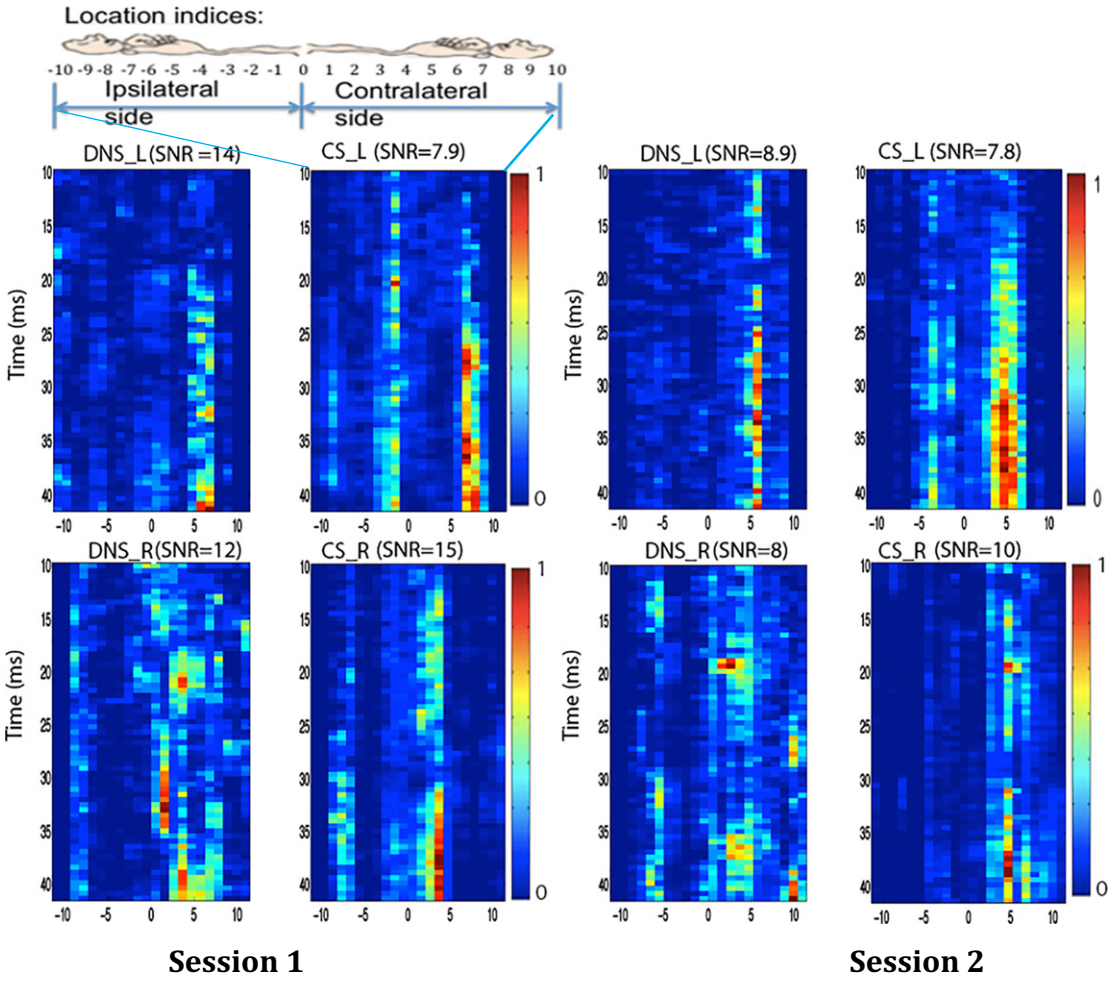

Fig. 4. Within-subject repeatability test on the able-bodied participant. The left and right subplots show the results obtained in session 1 and session 2, respectively. The color represents the normalized strength obtained at a specific time (y-axis, from 10 to 40 ms with 0 representing the onset of the stimulation) and location (x-axis, with negative and positive 1–10 indicate segments on ipsilateral and contralateral side S1, respectively, all from medial to lateral). In this figure, CS means cutaneous stimulation, and DNS means direct nerve stimulation.

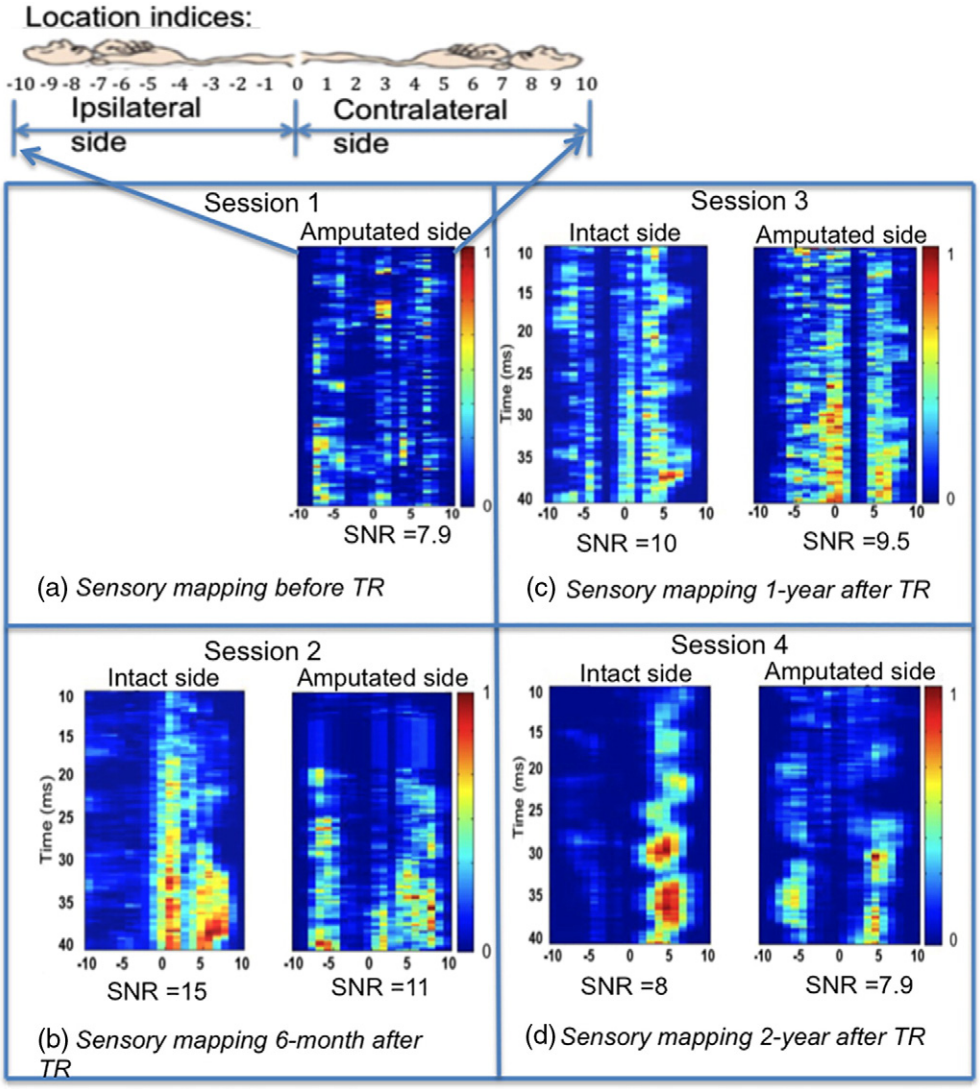

Fig. 5. Sensory cortical mapping of different sites of the upper limb following amputation and TR.

activity resulting from finger stimulation in the able-bodied participate has a more focused pattern in the contralateral S1 as compared to the ipsilateral S1, as suggested by the averaged ellipse, in the most right part of Fig. 6 having a larger size in the vertical direction than that in the horizontal direction. This averaged ellipse is located at the averaged peak location and with an averaged size from all different stimulations over two sessions in this able-bodied participant. This averaged result, marked by a green open ellipse, was used as the reference to compare results between the amputee and the able-bodied participant.

3.2. Results from the intact side in the amputee participant

Results from the intact side in the amputee participant are shown in the left plots in Fig. 5b–d and by the blue dotted ellipse in Fig. 6. As shown in Fig. 6, the peak locations of cortical responses to stimuli from the intact middle finger in the amputee participant on different sessions were not as consistent as compared to the results from able-bodied control participant. At 6 months after TR (session 2), we observed medial-shifted activity for the intact middle finger from the contralateral S1 with a relatively lower contralateral *Q*-value (i.e., the vertical size of the blue dotted ellipse in Fig. 6 is smaller as compared to the vertical size of the 'averaged green ellipse'). This *Q*-value stayed low at 12 months after TR, but with the peak back to the 'normal' hand area, suggesting a relatively diffused pattern of activation with a 'normal' center location. Two years after the TR, the peak stayed inside the hand area but now with a comparably 'normal' *Q*-value, again as compared to the 'average green ellipse' obtained from the control subject. At 2 years after TR, minimal activity was observed over the ipsilateral S1 when stimulating the intact finger, as suggested by a low *Q*-value from the ipsilateral S1.

3.3. Results from the amputated side in the amputee participant

Results from the amputated side in the amputee participant are shown in the right plots in Fig. 5a–d and the red solid ellipse in Fig. 6, which varied a lot on different sessions. Results from stimulating the residual median nerve before TR showed a diffuse bilateral pattern without clear focus in either time or spatial domains, as shown in the right plot in Fig. 5a, and also indicated by the low *Q*-values from both ipsilateral and contralateral S1.

Six months and 1 year after TR, the responses of stimulating the residual median nerve showed bilateral spatial patterns on S1, with increased foci in both spatial and time domains as compared to before TR results. In the spatial domain, both distributions (6 and 12 months after TR) showed two foci, and with the contralateral one on the 'normal' hand/finger area (index 5). The activity at the 6 months post surgical mark has a second peak in ipsilateral center at finger/hand position (index −5); while at 1 year after TR, the second activity center shifted

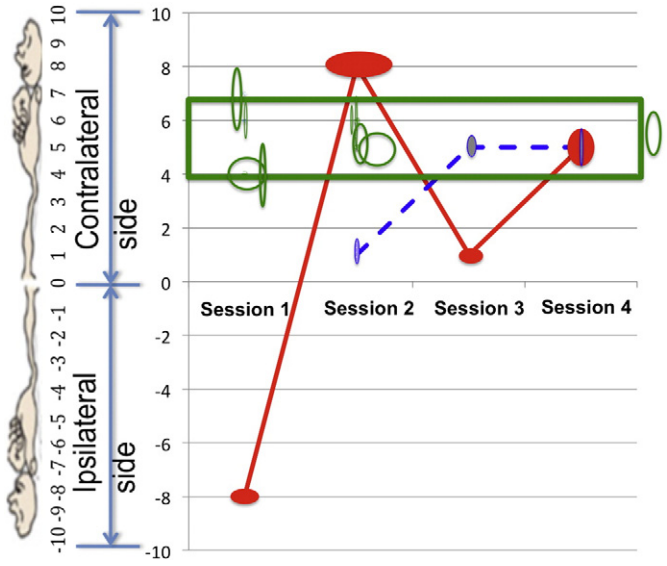

Fig. 6. The peak locations and *Q*-values for each stimulation site on different days for both subjects. In this figure, results from finger or finger nerve are represented by ellipses. Symbols in green open, blue dotted and red solid represent results from able-bodied control participant, and from amputee participant's intact and amputated sides, respectively. The center of the ellipse represents the peak location on the bilateral S1 cortices. The vertical and horizontal sizes of each of the ellipses represent the *Q*-values from the contralateral and ipsilateral S1, respectively. The green box shows the range in which the results obtained from able-bodied control subject were obtained, and the green ellipse to the right of the green box shows the averaged location and size of the all the ellipses from the able-bodied over two different stimulation sites and two sessions. In the figure legend, DNS and CS indicate direct nerve and cutaneous stimulation, respectively. A focused cortical activity at the finger area is expected to result in an ellipse located at about the +5 location and with a large vertical size and a small horizontal size.

to the contralateral shoulder position (index 1). Furthermore, activities from both sessions 2 and 3 still have a relatively larger *Q*-value in ipsilateral S1 as compared to that from contralateral S1 (i.e., the ellipses have a longer horizontal size on sessions 1, 2 and 3), suggesting that the activity from contralateral S1 is more diffused than that from ipsilateral S1.

Two years after TR, we observed even more focused cortical activity in both time and spatial domains (Fig. 5d). In this figure, we see strong activity during 26–40 ms on bilateral S1 finger position (index 5 and −5) with stronger activity found in the contralateral S1. Both the location and time delay of this strong contralateral activity are consistent with that obtained by stimulating the intact middle finger. However, the stimulation of the intact index finger shows activity only over the contralateral S1, while results obtained by stimulating the corresponding location from the amputated side still showed moderate activity from the ipsilateral S1. Finally, 2 years after TR, for the first time a more focused activity pattern was obtained over the contralateral S1, with the vertical size of the ellipse comparable to that of the 'averaged green ellipse' and to the blue dotted ellipse resulting from stimulating the intact middle finger at that time. In short, 2 years after TR, both the peak location and the *Q*-values fell inside the 'normal' range.

4. Discussions and conclusions

4.1. Sensory cortical reorganization after amputation and TR

4.1.1. Cortical reorganization for the amputated side

Our results from one individual with a trans-humeral amputation provide a single case study for long-term plasticity of sensory cortical representations following peripheral injury and targeted reinnervation. About 1 year after amputation and before TR, we found that the cortical representation of the residual median nerve showed a diffuse pattern without clear focus in either spatial or time domains. All results are consistent with previous findings from animals and human studies (Wall et al., 1986; Bjorkman et al., 2007a,b).

Focused cortical activity in the time domain was first observed 6 months after TR, and then consistently appeared in the results obtained 1 and 2 years post-TR. In the spatial domain, we observed a bilateral somatosensory representation evoked by stimulating the residual median nerve from all of the 3 post-TR experiments, with more diffused pattern during the first 2 post-TR experiments. The diffused pattern may explain why the participant, in addition to strongly feeling his missing middle finger, also faintly felt his elbow and thumb.

Two years post-TR, we observed bilateral cortical sensory representations on S1, with strong and focused activity on the contralateral side and moderate and less focused activity on the ipsilateral side, all with centers over the finger/hand area (indices: −5 and 5), suggesting that sensory representation of the reinnervated median nerve returned to a close-to-normal pattern.

4.1.2. Cortical reorganization for the intact side

Besides the changes in the cortical representation for the amputated finger, we also found that cortical representation for the intact finger was altered during the first 2 years following TR. The overall trend is also returned to 'normal' pattern, i.e., the peak location getting closer to the normal position and with higher focus in the contralateral S1.

4.1.3. Time course of sensory cortical reorganization after TR

Our results showed similar changes of the spatial pattern as that reported previously following hand replantation. In these previous reports, about 1 month after immediate surgical replantation that repaired the injured nerve, an ipsilateral cortical representation of the missing hand was observed. The sensory mapping of the replanted hand was then shifted to a bilateral pattern about 4 months after the replantation, and back to a predominantly contralateral representation about 8 months after the replantation (Bjorkman et al., 2007a). This suggests that TR has a similar effect on the cortical reorganization as immediate replantation. However, the return of a predominantly contralateral representation took about 2 years after TR, which is slower than the progress after hand replantation. The longer recovery phase of sensory representation after TR, as compared to after replantation, may be due to the fact that hand replantation was performed immediately after injury, while TR was performed 1 year after amputation in this participant. In the former case, there may not have been enough time between the injury and replantation to generate significant cortical sensory remapping. However, in our case, we showed that the cortical representation of the missing finger was already difficult to identify in either the time or spatial domains. Lastly, our results demonstrated that even over a year after the amputation, the sensory cortex still preserved its plasticity — this means that cortical sensory mapping following amputation can potentially be reversed following interventional procedures such as TR.

In short, these results demonstrate that TR-induced cortical sensory remapping starts to have clear foci on hand/finger area in S1 no longer than 6 months after TR. About 2 years after TR, the new sensory maps for the missing part (e.g. the middle finger) return closer to the original locations. This cortical reorganization is associated with the previous reported return of the cutaneous sensation following TR (Kuiken et al., 2007a; Marasco et al., 2009). The return to a normal pattern for the intact finger stimulation occurred about at 1 year after TR, which was earlier than that for the amputated side.

4.2. Possible reasons for the cortical reorganization following amputation and TR

The lack of a clear pattern of activation in both time and spatial domains after amputation and before TR may be related to the

withdrawal of axons from thalamus and cortex in response to peripheral somatosensory denervation (Graziano and Jones, 2009).

Since the majority of somatosensory pathways terminate at contralateral S1, previous work constrained their analysis in the contralateral hemisphere (Blume et al., 2014). Our results show bilateral activity in both the able-bodied and amputee participants. Although stronger and more focused activity in the contralateral S1 was obtained in the able-bodied subject, this was not the case in the amputee participant. Bilateral cortical activity was also reported in another study of an amputee participant (Bjorkman et al., 2007a,b). However, none of the previous reports explain the neuroscientific basis for this bilateral activity over the sensory cortices. We believe that this bilateral activity may be related to activation of sensory pathways via the reticular formation, which results in bilateral projections to the sensory cortices. Although we used stimulation with an intensity lower than the motor threshold, it may still have resulted in activation of some crude touch sensation via A-delta and C fibers when we stimulated the skin or the nerve (Del Gratta et al., 2002). These A-delta and C fibers project via the reticular formation and the thalamus to bilateral somatosensory cortices, as supported by the existence of both uncrossed and modest crossed thalamocortical projections, as seen in primates (Preuss and Goldman-Rakic, 1987). An additional explanation is that projections to the contralateral somatosensory cortex result in bilateral representations of hands/arms and shoulder via interhemispheric interactions (Iwamura et al., 1994, 2002).

Concurrently, we also see medial activation in both able-bodied and amputee participants. Medial activation may be caused by the overlap in representation of different parts of the limb on S1 (Woolsey et al., 1979; Nii et al., 1996; Maldjian et al., 1999). Due to this overlap, when examining the representation of a single part of the limb, it is possible that cortical responses in multiple parts of S1 can be seen.

It is worth noting that results in the able-bodied subject from every single experiment showed a peak location at hand/finger area on contralateral S1 and with a more focused pattern at the contralateral S1 as compared to that over the ipsilateral S1. Such consistency is not seen in the amputee participant. Shortly after amputation and TR surgery, the activity in the ipsilateral S1 via spinoreticular pathways may be enhanced, due to the reduced sensory stimulation via the dorsal columns and the spinothalamic sensory pathways. Therefore, the enhanced ipsilateral activity may suggest an initial adaptive strategy following amputation and TR.

Less focused activity can also be caused by low signal to noise ratio (SNR). We compared SNR of able-bodied participant from different methods and on different days (ranging from 7.8 to 15) to that of the amputee participant (ranging from 7.9 to 15). No significant difference in SNR between the two subjects was found. Therefore, the SNR cannot explain the consistency in the primary activity in the contralateral S1 in the able-bodied participant versus the highly varied locations and *Q*-values in the amputee participant.

The ipsilateral activity in the amputee participant may also be explained by phantom pain. However, the subject reported almost no phantom pain, thus this possibility is not a likely contributing factor either.

Furthermore, since we did not include a control participant who had a similar amputation but underwent no TR surgery, we therefore cannot totally exclude the possibility that the return to 'normal' representation is at least partially related to 'natural' reorganization subsequent to the loss of a part of the upper limb. However, most previous studies support a cortical remapping immediately following amputation, and not enough evidence suggests that a return of the 'normal' cortical activity would occur 'naturally'.

It is also worth noting that our results are limited to only one single amputee participant and with the last experiment using a cutaneous stimulation versus the previous 3 experiments using direct nerve stimulation. In order to validate our methods, experiments using both stimulation methods were conducted in an age-matched able-bodied control participant on different experimental sessions, to evaluate errors caused by different methods and different sessions. Results on this able-bodied control participant are consistent, with the resulted peak locations always within the finger/hand areas on the contralateral S1 (indices from 4 to 7). These results gave us confidence in the ability to evaluate changes of cortical sensory maps in the participant who underwent a trans-humeral amputation and subsequent targeted reinnervation.

Finally, it is interesting to note that the return to the 'normal' hand/finger area over the contralateral S1 cortex mirror results obtained in the reconstitution of 'normal' motor maps following TR as reported in a previous study (Chen et al., 2013).

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